

IL-17A (-197G/A) and *IL-17F* (7488T/C) gene polymorphisms and cancer risk in Asian population: a meta-analysis

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Abstract: Interleukin (IL)-17 has been shown to play an important role in the pathogenesis of inflammation and cancer. The *IL-17A* (-197G/A) and *IL-17F* (7488T/C) polymorphisms have been extensively investigated with cancer risk, but individually published results have been inconclusive. The aim of this study was to clarify the effects of the *IL-17A* (-197G/A) and *IL-17F* (7488T/C) polymorphisms on cancer risk in Asian populations. Relevant studies were identified by searching databases extensively. The association between the *IL-17A* (-197G/A) and *IL-17F* (7488T/C) polymorphisms and cancer risk was assessed by odds ratios (ORs) together with their 95% confidence intervals (CIs). A total of 12 articles with adequate information satisfied our inclusion criteria; these included 12 studies, with 4,540 cases and 5,875 controls, of *IL-17A* (-197G/A) polymorphism and seven studies, with 1,960 cases and 3,226 controls, of *IL-17F* (7488T/C) polymorphism. In the overall analysis, the *IL-17A* (-197G/A) polymorphism was significantly associated with increased cancer risk ($P < 0.05$), for all genetic models. However, there was no statistically significant association between *IL-17F* (7488T/C) and cancer risk ($P > 0.05$), for any genetic models. Furthermore, stratification by cancer type revealed a significant correlation between the *IL-17A* (-197G/A) polymorphism and cancer risk for all cancer types. When stratified by source of controls, a significant correlation was observed between the *IL-17A* (-197G/A) polymorphism and cancer risk in the population-based control subgroup but not in hospital-based control subgroup. In conclusion, our meta-analysis provides evidence that the *IL-17A* (-197G/A) polymorphism might be associated with cancer risk, while no evidence suggested a significant association between *IL-17F* (7488T/C) polymorphism and cancer risk.

Keywords: interleukin-17, meta-analysis, cancer, polymorphism

Introduction

Interleukin (IL)-17A, initially termed as cytotoxic T lymphocyte-associated antigen (CTLA)-8, is the founding member of IL-17 cytokine family, consisting of six homologous proteins (from IL-17A to IL-17F).¹ IL-17 is a pleiotropic cytokine that acts on multiple cell types to enhance the production of proinflammatory molecules, including the induction of IL-6, IL-8, and prostaglandin E₂, as well as enhancing granulocyte colony-stimulating factor and CXC chemokine production.^{2,3} In addition, IL-17 induces secretion of tumor necrosis factor (TNF)- α , IL-1 β , and stromelysin, by macrophages,^{4,5} and activates the nuclear factor κ B and activator protein 1 transcription factors, which may explain its proinflammatory properties.^{6,7}

Recently, several studies have shown that IL-17 can have either a protumor or antitumor role in different cancer models.⁸ Accumulating evidence indicates that IL-17

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expression is aberrant in several human tumors, such as ovarian cancer,⁹ cervical cancer,¹⁰ breast cancer,¹¹ hepatocellular carcinoma,¹² esophageal cancer,¹³ gastric cancer,¹⁴ and colorectal cancer.¹⁵ But the underlying mechanism of IL-17 in tumor initiation and progression is not yet completely clear. Of note, Kryczek et al suggested that endogenous IL-17 or/and T helper (Th)17 cells may play a protective role in tumor immunity.¹⁶ Martin-Orozco et al reported that IL-17A-deficient mice were more susceptible to developing lung melanoma.¹⁷ These studies showed an opposite role of IL-17; specifically, they suggest an antitumor effect, by promoting cytotoxic T lymphocyte generation.

A large number of previous studies have suggested the possible correlation between genetic polymorphisms of cancer susceptibility genes and higher risk of human malignant tumors. There are several single nucleotide polymorphisms (SNPs) that are reported for the *IL-17* gene, and the *IL-17A* gene polymorphism *IL-17A* (-197G/A, rs2275913) and *IL-17F* gene polymorphism *IL-17F* (7488T/C, rs763780) are reported to be associated in gastric carcinogenesis.¹⁸ *IL-17A* (-197G/A), located at a position -197 from the starting codon of the *IL-17A* gene, may regulate the expression of messenger ribonucleic acid (mRNA).¹⁹ Recently, Kawaguchi et al reported that *IL-17F* (7488T/C) causes a histidine (His)-to-arginine (Arg) substitution at amino acid 161 (H161R) variant.²⁰ To date, many studies have been published that assessed the association between the *IL-17A* (-197G/A) and *IL-17F* (7488T/C) polymorphisms and cancer susceptibility, but they have reported controversial results. A single case-control study may fail to completely demonstrate the complicated genetic relationship because of the small sample size.²¹ In order to provide strong evidence of the effects of the *IL-17A* (-197G/A) and *IL-17F* (7488T/C) polymorphisms on cancer susceptibility, we performed a meta-analysis, by combining data from numerous published studies.

Materials and methods

Search strategy

A comprehensive literature search of PubMed, Embase, Web of Science, Science Direct, SpringerLink, and the Chinese National Knowledge Infrastructure databases (up to November 2013) was conducted to identify case-control studies that investigated the association between *IL-17* polymorphisms and cancer risk. The search strategies were based on combinations of the following keywords: “cancer or carcinoma or neoplasm or tumor” AND “IL-17 or IL-17A or IL-17F or CTLA” AND “polymorphism or variant or mutation or genotype”. There was no restriction on time period,

sample size, population, or language, in order to minimize potential publication bias.

Selection criteria

Studies were included in the meta-analysis if they satisfied the following inclusion criteria: 1) case-control studies focused on association between the *IL-17A* (-197G/A) or *IL-17F* (7484T/C) polymorphism and cancer risk; 2) study design that was either retrospective or a nested case-control design; 3) any diagnoses of patients with cancer had to be confirmed by pathological examinations; and 4) sufficient published data to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI). The exclusion criteria of the meta-analysis were: 1) case-control studies not focusing on the correlation between the *IL-17A* (-197G/A) or *IL-17F* (7484T/C) polymorphism and cancer risk; 2) studies with duplicate data; 3) studies with incomplete data; and 4) meta-analyses, letters, reviews, and editorial articles. When an individual author published several articles obtained from the same patient population, only the newest or most complete article was included in the analysis.

Data extraction

Two authors independently extracted data from the included studies (Dai and Zhou). For each eligible study, the following information was extracted: first author's name, year of publication, country, ethnicity, cancer type, numbers of cases and controls, source of controls (hospital-based controls or population-based controls), genotyping method, and the Hardy-Weinberg equilibrium frequency. In cases of discrepancy, a consensus was reached by consulting a third author.

Sensitivity analysis

Sensitivity analysis was employed by sequentially excluding a single study each time, in an attempt to identify the potential influence of the individual data set to the pooled ORs.²²

Statistical analysis

Data management and processing were performed using Review Manager (RevMan) 5.0 software (The Nordic Cochrane Centre, Copenhagen) and Stata 11.0 (Stata Corp, College Station, Texas, USA). The strength of the association between the *IL-17* gene polymorphisms and cancer risk was measured by crude ORs and 95% CIs. The significance of the combined ORs was determined by a Z test, and two-sided *P*-value <0.05 was considered significant. The pooled ORs were calculated for the allele model (mutation [M] allele versus [vs] wild [W] allele), dominant model (WM + MM vs WW), recessive model

(MM vs WM + WW), homozygote comparison (MM vs WW), and heterozygote comparison (WM vs WW), respectively. Stratified analyses were conducted with respect to cancer type and source of controls. Statistical heterogeneity among the studies was evaluated using the chi square-based Q -test, and heterogeneity was considered significant when $P < 0.1$ for Q statistic. Heterogeneity was quantified by I² statistics examining the percentage of heterogeneity (0%–25% = no heterogeneity; 25%–50% = moderate heterogeneity; 50%–75% = large heterogeneity; and 75%–100% = extreme heterogeneity).²³ The random effects model was used when heterogeneity was significant ($I^2 > 50\%$ or $P \leq 0.10$); otherwise, the fixed effects model was used. Publication bias was examined with both Begg's funnel plot²⁴ and the Egger's regression method,²⁵ and $P < 0.05$ was considered representative of statistically significant publication bias.

Results

Characteristics of eligible studies

A total of 136 relevant studies were reviewed based on our selection strategy. The stepwise selection process is shown in Figure 1. After sequential selection, a total of 12 articles with adequate information satisfied our inclusion criteria, among which were 12 studies, with 4,540 cases and 5,875 controls, of the *IL-17A* (-197G/A) polymorphism^{18,26–36} and seven studies, with 1,960 cases and 3,226 controls, of the *IL-17F* (7488T/C) polymorphism^{18,29,31–34,36}. All studies were case-control designs, with subjects of Asian ancestry. Out of the 12 applicable studies, eight were studies of gastric cancer, one was cervical cancer, one was breast cancer, one was ovarian cancer, and one was bladder cancer. Population-based controls were used in seven studies, and hospital-based

controls were used in five studies. The detailed characteristics of the eligible studies are listed in Table 1. The genotype distribution of *IL-17* polymorphisms in the controls was in compliance with Hardy–Weinberg equilibrium, except for two studies of *IL-17A* (-197G/A) polymorphism^{18,34} and three studies of *IL-17F* (7488T/C) polymorphism.^{30,32,33}

Quantitative data synthesis

IL-17A (-197G/A) polymorphism

The results of the meta-analysis are presented in detail in Table 2. For the *IL-17A* (-197G/A) polymorphism, 12 studies were combined. In the overall analysis, a significant association between *IL-17A* (-197G/A) polymorphism and cancer risk was found under the allele model (OR = 1.23, 95% CI = 1.10–1.38, $P < 0.01$), dominant model (OR = 1.22, 95% CI = 1.08–1.37, $P < 0.01$), recessive model (OR = 1.50, 95% CI = 1.17–1.93, $P < 0.01$), homozygous comparison (OR = 1.62, 95% CI = 1.27–2.06, $P < 0.01$), and heterozygous comparison (OR = 1.11, 95% CI = 1.01–1.21, $P = 0.03$).

Subgroup analysis, stratified by cancer type, also suggested a significant association between *IL-17A* (-197G/A) polymorphism and cancer risk in the gastric cancer subgroup, under the allele model (OR = 1.22, 95% CI = 1.06–1.41, $P < 0.01$), dominant model (OR = 1.17, 95% CI = 1.02–1.33, $P = 0.03$), recessive model (OR = 1.58, 95% CI = 1.11–2.24, $P < 0.01$), and homozygous comparison (OR = 1.61, 95% CI = 1.17–2.23, $P < 0.01$). Moreover, a significant association was observed in the other cancer subgroups, under any of the genetic models ($P < 0.05$) (Table 2 and Figure 2A). Therefore, no difference was observed between the cancer types.

Stratified analyses by the source of control also suggested that *IL-17A* (-197G/A) polymorphism increased the cancer risk in the population-based control subgroup, under all genetic models (allele model: OR = 1.24, 95% CI = 1.08–1.41, $P < 0.01$; dominant model: OR = 1.21, 95% CI = 1.09–1.33, $P < 0.01$; recessive model: OR = 1.41, 95% CI = 1.08–1.82, $P = 0.01$; homozygous comparison: OR = 1.53, 95% CI = 1.17–2.01, $P < 0.01$; and heterozygous model: OR = 1.15, 95% CI = 1.02–1.28, $P = 0.02$). In contrast, a significant association was only found under homozygous comparison (OR = 1.65, 95% CI = 1.08–2.52, $P = 0.02$) in the hospital-based control subgroup (Table 2 and Figure 2B).

IL-17F (7488T/C) polymorphism

For the *IL-17F* (7488T/C) polymorphism, seven studies were combined. When all seven studies were pooled into the meta-analysis, there was no significant association between

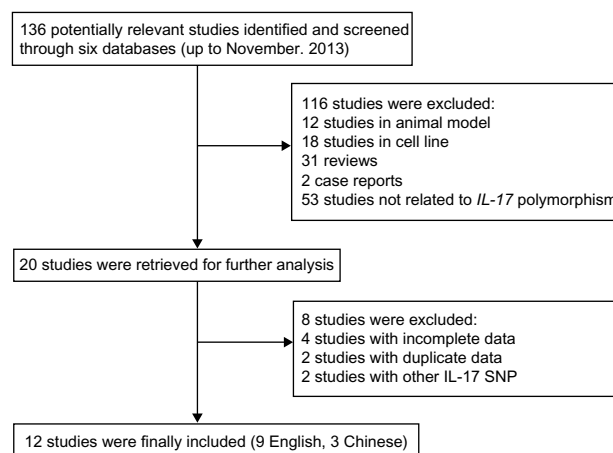


Figure 1 Flow chart of the literature search and study selection.

Abbreviations: IL, interleukin; SNP, single nucleotide polymorphism.

Table I Characteristics of studies included in the present meta-analysis

Studies	Year	Country	Ethnicity	Cancer type	Source of controls	Sample size	SNP studied	Conclusion	Genotyping method	HWE
Arisawa T ¹⁹	2012	Japan	Asian	Gastric	HB	337/587	<i>IL-17A</i> (-197G/A)	<i>IL-17A</i> (-197G/A) (+)	PCR-SSCP	0.080
Quan Y ²⁷	2012	People's Republic of China	Asian	Cervical	PB	311/463	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (+) <i>IL-17F</i> (7488T/C) (-)	Taqman® (Applied Biosystems, ABI, Foster City, CA, USA)	0.433; 0.064
Rafiei A ²⁸	2013	Iran	Asian	Gastric	PB	161/171	<i>IL-17A</i> (-197G/A)	<i>IL-17A</i> (-197G/A) (+)	PCR-RFLP	0.491
Shibata T ¹⁸	2009	Japan	Asian	Gastric	HB	287/523	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (+) <i>IL-17F</i> (7488T/C) (-)	PCR-SSCP	<0.01; 0.457
Wang L ²⁹	2012	People's Republic of China	Asian	Breast	PB	491/502	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (-) <i>IL-17F</i> (7488T/C) (-)	SNaPshot® SNP assay (Applied Biosystems)	0.173; 0.775
Wu X ³⁰	2010	People's Republic of China	Asian	Gastric	PB	1,010/1,500	<i>IL-17A</i> (-197G/A)	<i>IL-17A</i> (-197G/A) (-)	PCR-RFLP	0.351
Yuan Y ³⁴	2012	People's Republic of China	Asian	Ovarian	HB	92/38	<i>IL-17A</i> (-197G/A)	<i>IL-17A</i> (-197G/A) (-)	PCR-RFLP	0.028
Zhou B ³¹	2012	People's Republic of China	Asian	Bladder	HB	301/446	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (+) <i>IL-17F</i> (7488T/C) (-)	Taqman	0.292; 0.060
Chen JJ ³⁵	2010	People's Republic of China	Asian	Gastric	PB	1,042/1,090	<i>IL-17A</i> (-197G/A)	<i>IL-17A</i> (-197G/A) (-)	Taqman	0.967
Luo Y ³⁶	2010	People's Republic of China	Asian	Gastric	HB	24/230	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (+) <i>IL-17F</i> (7488T/C) (+)	PCR-RFLP	0.135; 0.747
Zhang X ³²	2013	People's Republic of China	Asian	Gastric	PB	260/512	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (+) <i>IL-17F</i> (7488T/C) (-)	MassARRAY® (Sequenom®, San Diego, CA, USA)	0.057; <0.01
Qinghai Z ³³	2014	People's Republic of China	Asian	Gastric	HB	311/611	<i>IL-17A</i> (-197G/A) <i>IL-17F</i> (7488T/C)	<i>IL-17A</i> (-197G/A) (+) <i>IL-17F</i> (7488T/C) (-)	MassARRAY	0.070; <0.01

Notes: (+) denotes there is significant association between *IL-17A* or *IL-17F* polymorphism and cancer risk. (-) denotes there is no significant association between *IL-17A* or *IL-17F* polymorphism and cancer risk.

Abbreviations: HB, hospital-based controls; IL, interleukin; HWE, Hardy–Weinberg equilibrium; PB, population-based controls; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; SSCP, sequence-specific primers.

the *IL-17F* (7488T/C) polymorphism and cancer susceptibility, under all genetic models (allele model: OR = 1.06, 95% CI = 0.89–1.26, $P=0.54$; dominant model: OR = 1.05, 95% CI = 0.85–1.29, $P=0.67$; recessive model: OR = 1.23, 95% CI = 0.87–1.75, $P=0.24$; homozygous comparison: OR = 1.24, 95% CI = 0.88–1.76, $P=0.22$; and heterozygous model: OR = 1.03, 95% CI = 0.82–1.29, $P=0.82$).

In the stratified analysis by cancer type, only the allele model (OR = 1.21, 95% CI = 1.01–1.44, $P=0.04$) displayed a significant association between *IL-17F* (7488T/C) polymorphism and cancer risk, in the gastric cancer subgroup. No significant association was found, under any genetic models, in the other cancer subgroup (all $P>0.05$) (Table 2 and Figure 3A).

Next, we performed a subgroup analysis according to the source of controls. The results showed that *IL-17F* (7488T/C) polymorphism was not associated with cancer risk, in either the

population-base control subgroup or the hospital-based control subgroup (all $P>0.05$) (Table 2 and Figure 3B). Therefore, differences in the controls did not affect the association between *IL-17F* (7488T/C) polymorphism and cancer risk.

Sensitivity analysis

The sensitivity analysis indicated that no single study influenced the pooled OR value, either for *IL-17A* (-197G/A) polymorphism or for *IL-17F* (7488T/C) polymorphism, suggesting that the results of this meta-analysis are stable (data not shown).

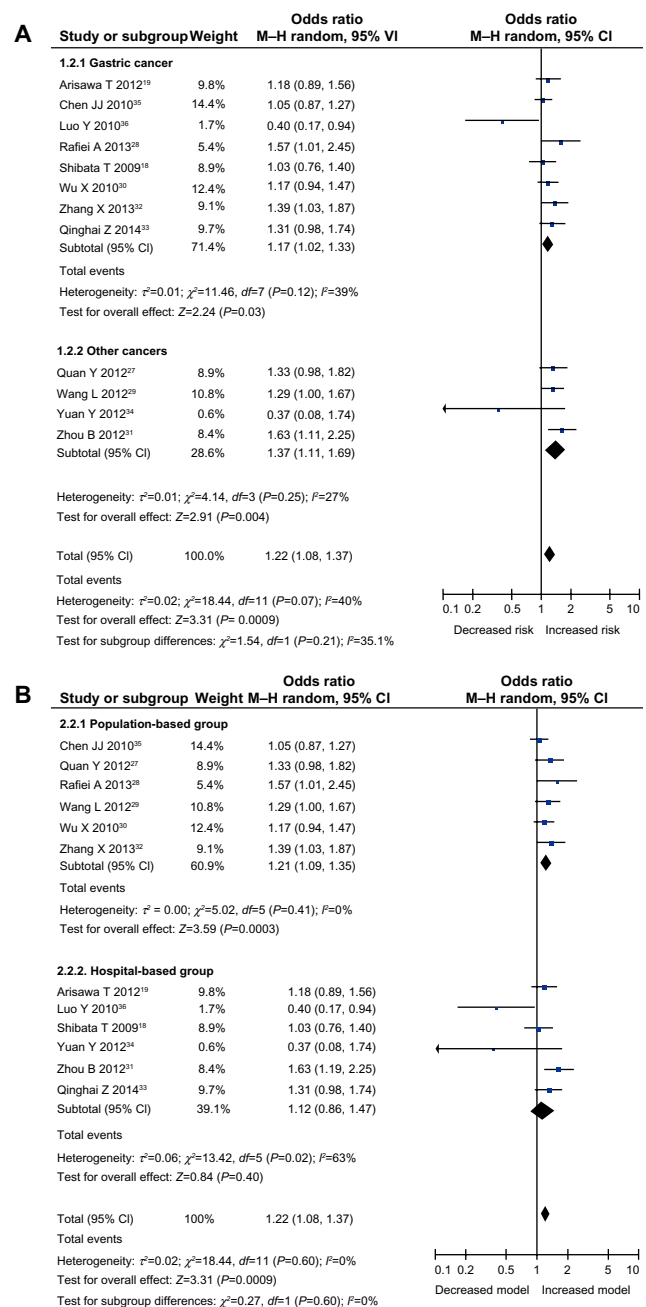
Publication bias

Publication bias of the selected articles was assessed using Begg's funnel plot and Egger's test. The shape of the funnel plot did not show an obvious publication bias for *IL-17A* (-197G/A) polymorphism or *IL-17F* (7488T/C) polymorphism (Figure 4A and B). Similarly, no evidence

Table 2 Meta-analysis of the IL-17A (-197G/A) polymorphism and IL-17F (7488T/C) polymorphism with risk of cancer

	Allele model		Dominant model		Recessive model		Homozygous comparison		Heterozygous comparison	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
IL-17A (-197G/A)										
Overall	1.23 (1.10–1.38)	<0.01	1.22 (1.08–1.37)	<0.01	1.50 (1.17–1.93)	<0.01	1.62 (1.27–2.06)	<0.01	1.11 (1.01–1.21)	0.03
Gastric cancer	1.22 (1.06–1.41)	<0.01	1.17 (1.02–1.33)	0.03	1.58 (1.11–2.24)	0.01	1.61 (1.17–2.23)	<0.01	1.06 (0.95–1.18)	0.28
Other cancers	1.27 (1.09–1.49)	<0.01	1.37 (1.11–1.69)	<0.01	1.42 (1.07–1.89)	0.02	1.69 (1.23–2.33)	<0.01	1.24 (1.04–1.48)	0.02
PB subgroup	1.24 (1.08–1.41)	<0.01	1.21 (1.09–1.33)	<0.01	1.41 (1.08–1.82)	0.01	1.53 (1.17–2.01)	<0.01	1.15 (1.02–1.28)	0.02
HB subgroup	1.19 (0.97–1.45)	0.09	1.12 (0.86–1.47)	0.40	1.52 (0.97–2.38)	0.07	1.65 (1.08–2.52)	0.02	1.03 (0.89–1.21)	0.68
IL-17F (7488T/C)										
Overall	1.06 (0.89–1.26)	0.54	1.05 (0.85–1.29)	0.67	1.23 (0.87–1.75)	0.24	1.24 (0.88–1.76)	0.22	1.03 (0.82–1.29)	0.82
Gastric cancer	1.21 (1.01–1.44)	0.04	1.20 (0.98–1.48)	0.08	1.30 (0.87–1.94)	0.20	1.33 (0.89–1.98)	0.17	1.18 (0.92–1.51)	0.19
Other cancers	0.91 (0.70–1.18)	0.47	0.89 (0.64–1.22)	0.46	1.04 (0.51–2.13)	0.90	1.02 (0.50–2.08)	0.96	0.88 (0.62–1.24)	0.46
PB subgroup	1.10 (0.93–1.30)	0.26	1.09 (0.90–1.32)	0.37	1.26 (0.78–2.03)	0.35	1.28 (0.79–2.06)	0.32	1.06 (0.87–1.30)	0.54
HB subgroup	1.04 (0.74–1.44)	0.84	1.04 (0.69–1.58)	0.84	1.21 (0.72–2.01)	0.47	1.21 (0.72–2.01)	0.47	1.05 (0.66–1.65)	0.85

Abbreviations: CI, confidence interval; HB, hospital-based controls; IL, interleukin; OR, odds ratio; PB, population-based controls; vs, versus.

**Figure 2** Meta-analysis to evaluate the association between the IL-17A (-197G/A) polymorphism and cancer risk (dominant model: AA + AG vs GG). (A) subgroup analysis by cancer type; (B) subgroup analysis by source of control.

Abbreviations: IL, interleukin; M-H, Mantel-Hanszel; vs, versus.

of publication bias was observed by Egger's test, for the IL-17A (-197G/A) dominant model ($P=0.270$) or the IL-17F (7488T/C) dominant model ($P=0.250$).

Discussion

Large-sample and unbiased, epidemiological studies of predisposition genes polymorphisms could provide insight to etiology of diseases. However, the findings are generally inconsistent, probably due to some limitation in these

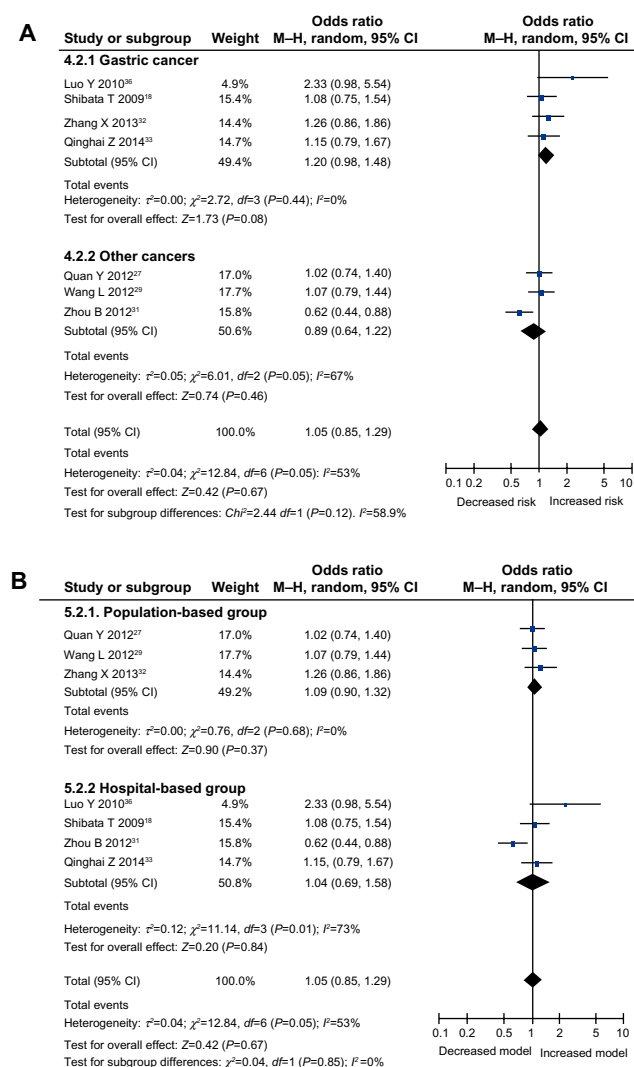


Figure 3 Meta-analysis to evaluate the association between the *IL-17F* (7488T/C) polymorphism and cancer risk (dominant model: CC + CT vs TT). (A) subgroup analysis by cancer type; (B) subgroup analysis by source of control.

Abbreviations: CI, confidence interval; IL, interleukin; vs, versus.

studies, such as small sample size, and mix of ethnicities and cancer types. Meta-analysis is considered a powerful tool for combining the contradicting results from different studies to achieve greater statistical power and obtain more reliable results than with a single study.³⁷ In this meta-analysis, we investigated the association between *IL-17A* (-197G/A) (rs2275913) and *IL-17F* (7488T/C) (rs763780) and cancer risk. Overall, our study provided evidence that *IL-17A* (-197G/A) polymorphism was associated with cancer susceptibility. However, no association was detected between *IL-17F* (7488T/C) polymorphism and cancer susceptibility. Sensitivity analysis and publication bias further strengthened the validity of these results.

IL-17 family members belong to a distinct category of cytokine and are involved in coordinating local tissue

inflammation, through release of proinflammatory and neutrophil-mobilizing cytokines.²⁰ To date, investigation into the function of the IL-17 cytokine family has been extensive, but the majority of the effort has focused on the role of two members, IL-17A and IL-17F. The *IL-17A* and *IL-17F* genes are both located at 6p12. In addition, among the IL-17 family, from the alignment of the amino acid sequences, IL-17A and IL-17F have the highest overall amino acid sequence identity and share similar functions in terms of their ability to induce chemokines, which are important in neutrophil recruitment and activation.³¹ IL-17A and IL-17F cytokines are both expressed by Th17 cells, which mediate chronic inflammation and cancer.⁹ Although the significance of IL-17A and -17F in the pathogenesis of the cancer has still remained unclear, we hypothesized that both the cytokines may affect the development of chronic inflammation followed by malignancy, coordinately or independently. Over the last several years, many studies have identified a variety of environmental, host immune status, and host genetic factors that play important roles in carcinogenesis. Moreover, Espinoza et al reported that *IL-17A* (-197G/A) polymorphism influences the response of the *IL-17* gene promoter to factors released in response to T cell activation, thus leading to a differential IL-17 production.³⁸ Kawaguchi et al revealed that *IL-17F* (7488T/C), which causes a His-to-Arg substitution at amino acid 161 (H161R) of IL-17F, lacked the ability to activate the mitogen-activated protein kinase pathway, cytokine production, and chemokine production, and blocked induction of IL-8 expression by wild type IL-17F in in vitro functional experiments.³⁹ Therefore, we evaluated the effect of the polymorphisms of two cytokines on cancer risk. Our investigation suggests that *IL-17A* (-197G/A), but not *IL-17F* (7488T/C), contributes to cancer susceptibility.

Subgroup analyses stratified by source of controls and cancer types were also performed. For *IL-17A* (-197G/A) polymorphism, a significant increased cancer risk was observed in gastric cancer and other cancers, suggesting that cancer type may not affect cancer susceptibility. Moreover, stratified analysis by source of controls suggested that *IL-17A* (-197G/A) polymorphism was associated with increased risk of cancer in the population-based control subgroup, but not in the hospital-based control subgroup. This may have been due to some selection biases existing in the hospital-based studies because such controls may have come from a population with a related disease and may not have been representative of the general population. For *IL-17F* (7488T/C) polymorphism, we found little association between *IL-17F* (7488T/C) polymorphism and cancer risk in subgroups analysis. This result

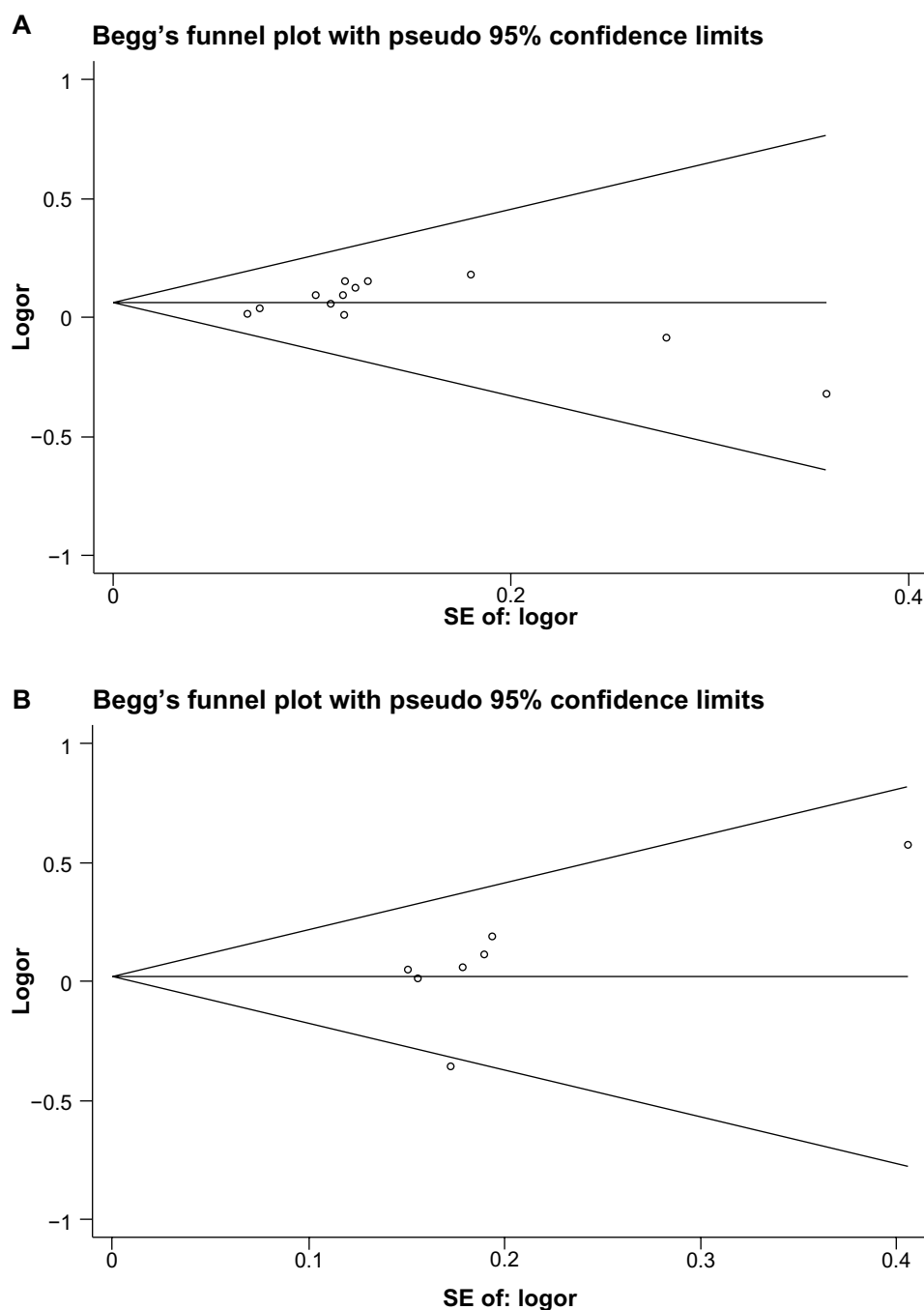


Figure 4 Funnel plots of *IL-17A* (-197G/A) polymorphism and *IL-17F* (7488T/C) polymorphism in the dominant model. **(A)** *IL-17A* (-197G/A) polymorphism; **(B)** *IL-17F* (7488T/C) polymorphism.

Abbreviations: IL, interleukin; SE, standard error of the mean.

indicates that the differences in cancer types and sources of controls do not affect cancer susceptibility.

Several potential limitations of the present meta-analysis should be acknowledged. First, significant heterogeneity was observed in the overall and subgroup analyses. Although two potential sources of the heterogeneity were investigated, including the source of controls and cancer types, neither of them sufficiently explained the between-study

heterogeneity. Second, the sample size is not large enough, especially for subgroup analysis. Thus, we do not have adequate power to evaluate the possible association for both polymorphisms, and the observed significant associations in some subgroup analysis may be not accurate. Third, the lack of observations concerning gene–gene and gene–environment interactions could have influenced our results. Fourth, only published studies were included in the

meta-analysis, and nonsignificant or negative findings may be unpublished. Hence, some inevitable publication biases might exist in the results.

Conclusion

In conclusion, our meta-analysis provides evidences that the *IL-17A* (-197G/A) polymorphism might be associated with cancer risk in the Asian populations, while no evidence suggested a significant association between the *IL-17F* (7488T/C) polymorphism and cancer risk. However, large-sample studies are warranted to validate our findings, especially in some types of cancer. More studies on gene–gene and gene–environment interactions should also be considered in the future, to obtain a more comprehensive understanding of the association between *IL-17* polymorphisms and cancer risk.

Acknowledgments

This work has been supported by Grants from the National Natural Science Foundation of China (No 81301835).

Disclosure

The authors report no conflicts of interest in this work.

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